REMARKS

This paper is in response to the non-final Office action mailed on July 14, 2009. In view of Applicants' Appeal Brief filed on March 9, 2009, prosecution has been reopened in this case and new grounds of rejection have been presented.

Entry and consideration of this amendment is respectfully requested. This paper is accompanied by a petition for a three month extension of time in which to respond and is therefore timely filed.

I. Status of the Claims

Claims 1-3, 6-16, 18, 19, 23, 24, 26 and 27 are pending.

II. Rejections Under 35 U.S.C. §103

Claims 1-3, 5-19, 23, 26, and 27 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Abbruscato, T.J., and Delgado, et al., or Ekwuribe.

These rejections are respectfully traversed for the reasons which follow.

Applicants' Claims

The claims are directed to a *hydrophilic* polymer-peptide conjugate, which, when administered into the blood circulation of a mammal, is capable of transport across the blood brain barrier. The conjugate consists of:

(i) a peptide that is either biphalin or [D-Pen^2, D-Pen^5] enkephalin (DPDPE),

(ii) covalently linked to one or more water-soluble polymer chains having a molecular weight from about 2,000 to about 100,000 daltons and selected from either poly(ethylene glycol) or copolymers of ethylene glycol and propylene glycol.

CITED ART

Abbruscato, TJ, et al., J. Pharmacol. Exp. Ther., 1996, Mar; 276(3):1049-57. Abbruscato is directed to the characterization and comparison of CNS (central nervous system) uptake and stability of biphalin, and two of its halogenated derivatives, p-{Cl-Phe^{4,4}}biphalin and p-{F-Phe^{4,4}}biphalin (Abbruscato, p. 1050, col 1, third full paragraph). The data provided in Abbruscato, as well as the reported conclusions, state that the increased passage of the chlorinated derivative of biphalin across the blood-brain barrier (BBB) is attributable to the molecule's *improved lipophilicity* due to the chloro-substituent at the p-Phe^{4,4} position. Conversely, a significant decrease in in-vitro permeability was reported for the fluoro-derivative. Abbruscato correlates the decrease observed for the fluoro-derivative with a *decrease* in lipophilicity (page 1054, col 1). In sum, Abbruscato suggests that structurally modified biphalin having *improved lipophilicity* demonstrates significantly improved passage across the BBB. In contrast, the Applicants' claims are directed to a *hydrophilic (*the exact opposite of lipophilic) conjugate of biphalin.

Delgado (Crit. Rev. Ther. Drug Carrier Syst., 1992; 9 (3-4); 249-304 is a review article describing various PEGylated ***proteins*** (not peptides such as biphalin or DPDPE) and their pharmacological properties, including methods of synthesis and analysis. Delgado has nothing to do with small peptides such as biphalin ((Try-D-Ala-Gly-Phe-NH)$_2$) or DPDPE (Tyr-D-Pen-Gly-Phe-D-Pen), and is completely silent regarding the impact of conjugation with a polyalkylene oxide on the ability of any compound, let alone a small peptide such as biphalin or DPDPE, to cross the BBB.

Ekwuribe (WO 01/19406) describes *amphiphilic* prodrugs comprising a drug such as etoposide joined by a hydrolyzable bond to PEG oligomers having from 1 to 25 polyethylene glycol subunits (page 7, lines 27-30). In the background section, Ekwuribe states that hydrophilic molecules require *an active transport system* to cross the BBB (page 2, lines 21-24). First, Ekwuribe is directed to *amphiphilic* prodrugs rather

than to hydrophilic conjugates. Second, the prodrugs of Ekwuribe possess small oligomeric PEGs with molecular weights ranging from 44 daltons (1 PEG monomer) to 1100 daltons (25 PEGs monomers). This is in complete and utter contrast to the water-soluble polymer chains recited in the Applicants' claims, having a molecular weight of from about 2,000 to about 10,000 daltons. Third, the conjugates encompassed by the Applicants' claims fail to encompass an active transport system - which is exactly why it is surprising that such conjugates exhibit transport across the BBB.

ARGUMENT

As reiterated by the Supreme Court in *KSR International Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1391(2007), the framework that still controls an objective analysis for determining whether claims are obvious is stated in *Graham v. John Deere* Co., 383 U.S. 1, 148 USPQ 459 (1966). Specifically, the Graham factors include:

(i) Determining the scope and content of the prior art;

(ii) Ascertaining the differences between the claimed invention and the prior art; and

(iii) Resolving the level of ordinary skill in the pertinent art.

In applying the Graham factors, both the claimed invention and the references must be considered as a whole. Finally, a prior art reference must be considered in its entirety, i.e., as a whole, *including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983).*

Rejection 1. Abbruscato combined with Delgado: First, in examining Abbruscato, this reference, even when combined with Delgado, fails to suggest the subject matter of the instant claims, and in fact, teaches away from them. Specifically,

Abbruscato teaches that in order to improve passive passage across the BBB over an unmodified drug such as biphalin, one must enhance the drug's lipophilicy. The instant claims recite just the opposite - i.e., a polymer-peptide conjugate that itself is hydrophilic and also capable, when administered into the blood circulation, of transport across the BBB. In no way would one skilled in the art, based upon the teachings of Abbruscato, expect a hydrophilic conjugate of biphalin to cross the BBB. The data shown in Fig. 3 of the Applicants' specification, i.e., that exemplary *hydrophilic* conjugates having the features recited in the claims exhibit *improved* analgesia over unmodified biphalin, is absolutely unpredictable based upon the teachings of Abbruscato.

In sum, the combination of Abbruscato and Delgado fails to render obvious the instant claims, since the combination fails to even remotely suggest the subject matter recited in the claims, and in fact, teaches the exact opposite.

Rejection 2. Ekwuribe: Turning now to Ekwuribe, this reference has no bearing on the patentability of the instant claims. Recalling the requirement to review the art as a whole, the conjugates of Ekwuribe are completely dissimilar from the conjugates recited by the Applicants. Ekwuribe describes amphiphilic prodrugs having small oligomeric PEGs covalently attached thereto. In contrast, the instant claims are directed to hydrophilic conjugates having significantly larger polyalkylene oxide chains attached thereto (having a molecular weight from about 2,000 to about 100,000 daltons). Finally, Ekwuribe suggests that an active transport system is required to facilitate transport of a hydrophilic drug across the blood brain barrier. The claimed conjugates lack such a transport system, as has been pointed out by the Applicant's on numerous prior occasions over the course of prosecution. That is to say, nowhere does Ekwuribe suggest or lead one of skill in the art to the subject matter embodied in the Applicants' claims.

In view of the above, it is submitted that the pending claims are non-obvious and comply with the standards of 35 U.S.C. §103. Withdrawal of the rejections of the claims under 35 U.S.C. §103 is therefore respectfully requested.

III. Conclusion

In view of the foregoing, the Applicants submit that all of the claims pending in the application patentably define over the art of record. A Notice of Allowance is therefore earnestly requested.

If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 590-1918.

Respectfully submitted,
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